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Open Access Review Article

Inflammation the Kingpin of Chronic Diseases Naturopathy as an alternative source of treatment: An updated overview

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ABSTRACT

Inflammation involves a sequence of events which can be categorized under three phases viz. acute transient phase, delayed sub-acute phase and chronic proliferate phase. Inflammatory mediators develop due to enhanced vascular permeability and leads to local edema. It is followed by the migration of leukocytes and phagocytes from blood to vascular tissues which is the second phase, in the third phase, tissue degradation is followed by fibrosis. There is a powerful link between chronic diseases and chronic inflammatory disorders. Chronic low-level inflammation contributes to the pathogenesis of these several diseases like Heart disease, Cancer, Chronic lower respiratory disease, Stroke, Alzheimer's, Diabetes, and Nephritis. The harmful side effects of synthetic drugs are numerous and there stands up the need of herbal drugs which are cost effective and free from side-effects. Several traditional ayurvedic phytomedicines have been used in the treatment of inflammatory disorders like *Ocimum sanctum*, *Hypericum peroratum*, *Boswellic serrata*, *Ficus racemosa* etc. which act as natural anti-inflammatory agents that can help in reducing the complications associated with chronic diseases.

Keywords: Inflammation, Chronic-low level inflammation, Cancer, Diabetes, Phytomedicines

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Introduction:

The word "inflammation", derived from the latin word "*inflammare*", (to set on fire), is a complex biological process which involve several chemical mediators which are induced by vascular tissue of the body, which when it comes in contact with several harmful stimuli like pollens, irritants, pathogens, and damaged cells. When human body is injured there occurs a series of chemical changes. Inflammation was prematurely considered as a single disease caused by disturbances of various fluids of the body. Nowadays, the modern concept of inflammation is a healthy process resulting from some disturbance or disease.

Table 1: Cardinal signs of Inflammation

Cardinal Signs of Inflammation				
Redness	**Heat**	**Swelling**	**Pain**	**Loss of Function**
Caused by dilation of arterioles / increased blood flow	Increased chemical activity and increased blood flow to skin surface	Caused by accumulation of blood and damaged tissue cells	Direct injury of nerve fibers, pressure on hematoma on nerve endings chemical irritants-bradykinin, histamine, prostaglandin	Increased pain/Swelling

Inflammation is frequently associated with pain, and involves occurrences such as the increase of vascular permeability, membrane alteration and increase of membrane permeability. When the injury is in the form of stress cells in the body are damaged by micro-organisms, physical agents or chemical agents. Inflammation of tissue is due to response to stress or free radicals. The humans' defensive response is characterized by redness, pain, heat and swelling and loss of function in the injured area. Loss of function depends on the site and extent of injury.

Inflammation is now recognized as an overwhelming burden to the healthcare status of human population and the underlying pathogenesis basis of a significant number of chronic diseases. Worldwide the annual mortality due to Chronic Inflammatory Diseases is expected to increase. By 2030, it has been estimated that 171 million people will be affected by chronic inflammatory diseases in the United States[1]. There is a strong link between chronic inflammatory conditions and chronic diseases. Chronic inflammation damages the cells of the brain, heart, arterial walls, and other anatomic structures and this damage leads to various inflammatory chronic diseases. Chronic low-level inflammation contributes to the pathogenesis of these several diseases like Heart disease, Cancer, Chronic lower respiratory disease, Stroke, Alzheimer's, Diabetes, and Nephritis (kidney inflammation).Inflammation produces complex biological changes of vascular tissues which are produced by harmful stimuli, such as pathogens, damaged cells, or irritants[2]. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogenic organism. However, inflammation is a stereotyped response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen[3]. Inflammation is part of a complex biological response to harmful stimuli.

Inflammation has been variously defined Houck (1963) as a vital response of tissue injury. Inflammation is the tissue reaction to infection, irritation or foreign substance. It is a part of the host defense mechanisms that are known to be involved in the inflammatory reactions such as release of histamine, bradykinin & prostaglandins. The development of non-steroids in overcoming human sufferings caused by inflammation such as Rheumatoid arthritis has evoked much interest in the extensive search for new drugs with this property[4]. Inflammation is a major component of the damage caused by autoimmune diseases and is also a fundamental contributor to diseases such as cancer, diabetes and cardiovascular disease[5].

The inflammatory process can also be defined as a sequence of events that occurs in response to noxious stimuli, infection or trauma[6]. The events of inflammation that underline these manifestations are induced and regulated by a large number of chemical mediators, including kinins, eicosanoids, complement proteins, histamine and monokines. Efficacy of anti-inflammatory agents in inflammatory states is indicated by their ability to inhibit the increase in the number of fibroblast during granular tissue formation[7].

Causes of inflammation:

The numerous causes of inflammation may be classified as

- **Microbes** e.g. bacteria viruses, protozoa, fungi
- **Physical agents** e.g. heat cold, mechanical injury ultra violet and ionizing radiation
- **Chemical agents** organic e.g. microbial toxins and organic poisons such as weed killers
- **Inorganic** e.g., acids and alkalies.

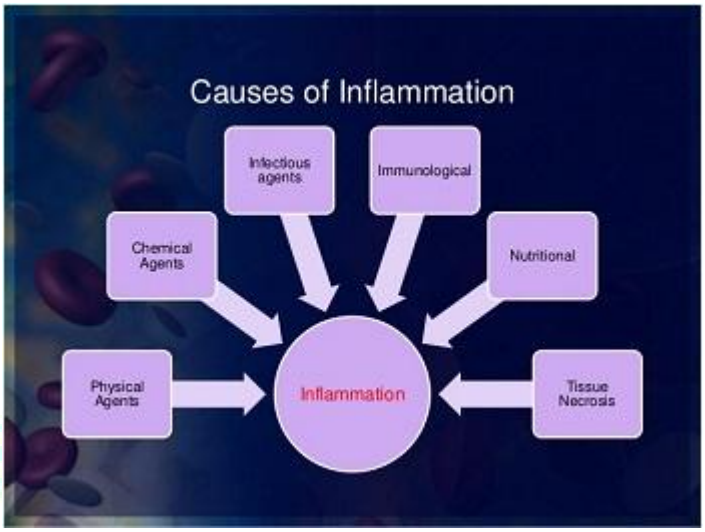

Figure 1: Causes of Inflammation

Mechanism of Inflammation:

Mechanism of inflammation is due to result of proinflammatory cytokines and chemokine release in response to injury or infection, mast cells in connective tissue as well as basophils, neutrophils and platelets leaving the blood from injured capillaries, release or stimulates the synthesis of vasodilators such as histamine, leukotrienes, bradykinins and prostaglandins. Certain products of complement pathways (C_5a and C_3a) can also trigger mast cells to release their vasodilators.

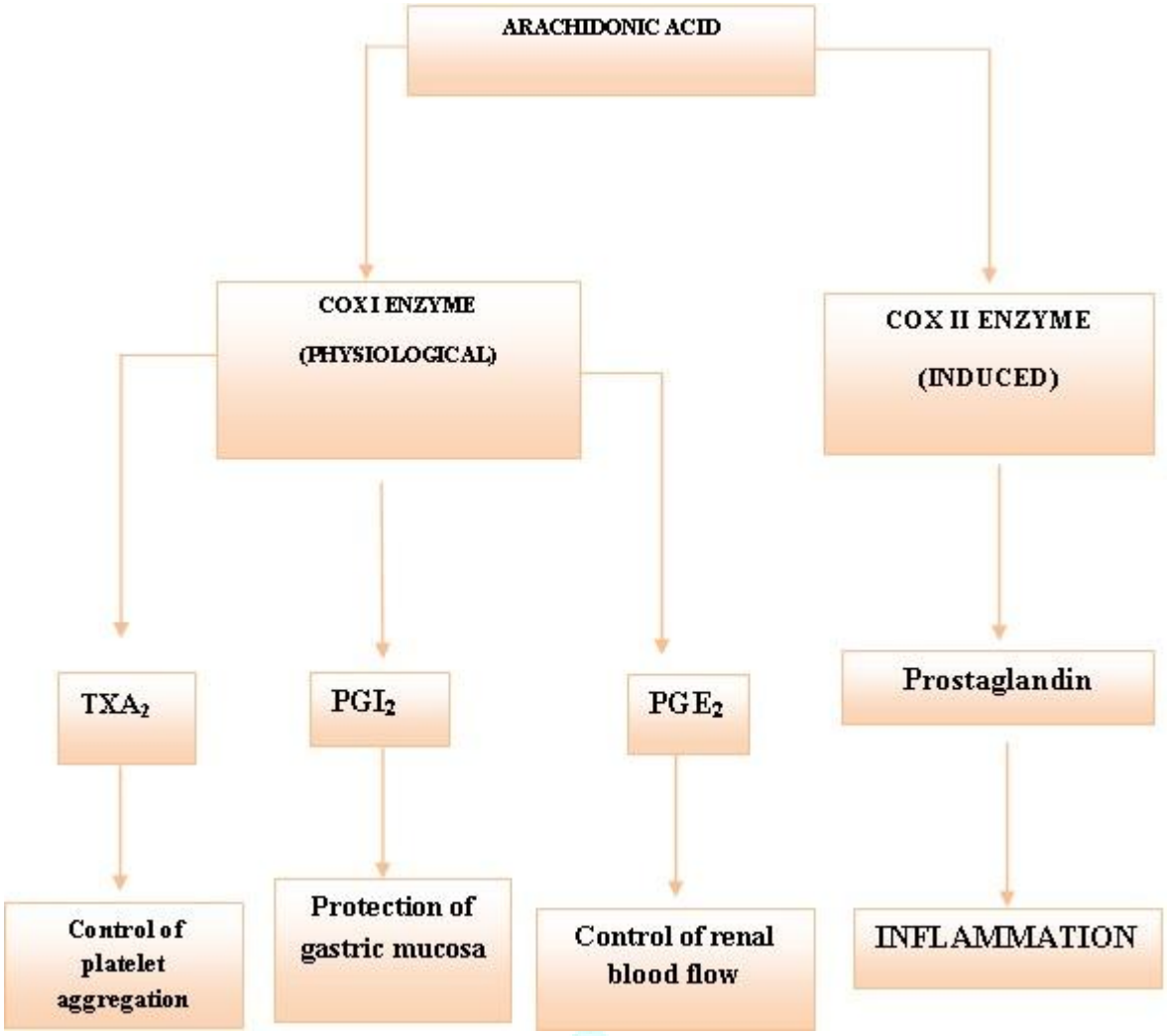

Figure 2: Diagrammatic Representation of the Prostaglandin Pathway

Diseases Associated with Chronic Inflammation:

Inflammation produces reactive oxygen species and reactive nitrogen species, which causes oxidative damage and further lead to chronic diseases[8]. These include heart disease, cancer, chronic lower respiratory diseases, stroke, Alzheimer's disease, diabetes, and nephritis.

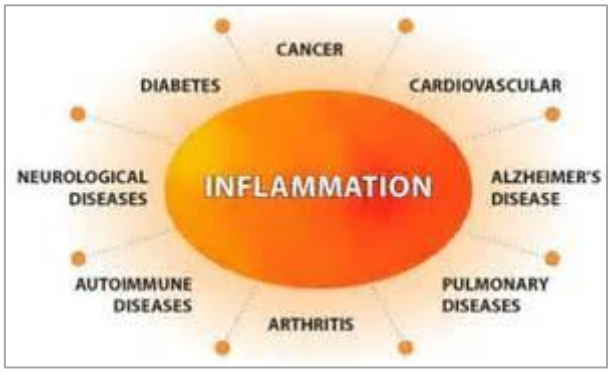

Figure 2: Diseases associated with Chronic Inflammation

- **Cardiovascular diseases (CVD)**

Inflammation is a fundamental part of atherosclerosis (oxidized low-density lipoprotein cholesterol evokes the inflammatory response). Circulating inflammatory cytokines are predictive of peripheral arterial diseases, heart failure, atrial fibrillation, stroke, and coronary heart disease.[9]C-Reactive Protein, an acute-phase protein are produced by the liver during bacterial infections and inflammation which was found to be a common marker for detecting cardiovascular and atherosclerotic diseases.[10]

- **Cancer**

Several studies reported the prominent links between chronic low-level inflammation and several types of cancers, including lymphoma, prostate, ovarian, pancreatic, colorectal and lung[11]. There are several mechanisms by which inflammatory mediators may contribute to pathogenesis of carcinogenesis, including alterations in gene expression, DNA mutation, epigenetic alterations, promotion of tumor vascularization, and the expression of pro-inflammatory cytokines that have roles in cancer cell proliferation.[12] Various pro-inflammatory mediators have been found to be elevated in several cancers. The pro-inflammatory biomarker STAT3 was found to be activated in 82% of patients with late-stage prostate cancer.[13,14,15] Another inflammatory transcription factor, NF-κB, was found in 60% of colorectal cancer patients. Also, the overproduction of cytokines has shown to be associated with cancer-related fatigue.[16]

- **Diabetes**

Inflammation is linked to diabetes and stands up insulin resistance. This fact has generated a growing interest in alternative anti-inflammatory therapies to slow down diabetes and complications associated with it. Nowadays,

diabetes is considered an inflammatory disease. The infiltration of macrophages into fat tissues and their subsequent release of pro-inflammatory cytokines into circulation occur at a greater rate in type II diabetics than in non-diabetics.[17,18] Pro-inflammatory cytokines clearly decrease insulin sensitivity and increase diabetic complications like nephropathy etc.[19]

- **Polycystic Ovarian Syndrome**

Chronic low grade inflammation has emerged as a key contributor to the pathogenesis of Polycystic ovarian syndrome. The proinflammatory cytokine tumor necrosis factor α is a known mediator of insulin resistance. Glucose stimulated TNF α release from MNC along with molecular markers of inflammation are associated with insulin resistance in PCOS. Increased abdominal adiposity is prevalent across all weight classes in PCOS and this inflammed tissue contributes to the inflammatory load in the disorder. According to 2009 study in the journal metabolism, levels of inflammatory markers in the blood are increased not only in overweight or obese women with PCOS but also in normal weight women thus supporting the fact that inflammation directly plays key role in PCOS.

- **Age-related macular degeneration (AMD).**

A study report of 11 population-based studies estimating over 41,000 patients demonstrated a clear association between elevated serum C-Reactive Protein levels (> 3 mg/L) and the incidence of late onset Age-related macular degeneration.[20]The risk of Age related macular degeneration in these high-C-Reactive Protein patients was increased over 2-fold compared with patients with CRP levels < 1 mg /L.

- **Osteoporosis.**

The Inflammatory cytokines like TNF-α, IL-1β, IL-6 are involved in normal bone metabolism. Osteoclasts, the cells that break down (resorb) bone tissue, are a type of macrophage and can be stimulated by pro-inflammatory factors. Systemic elevations in pro-inflammatory cytokines push bone metabolism towards resorption, and have been observed to induce bone loss in persons with periodontal diseases, pancreatitis, inflammatory bowel diseases, and rheumatoid arthritis.[21] An increase in the levels of inflammatory cytokines is also a mechanism by which menopause stimulates bone loss.

- **Cognitive decline**

Several observational studies reported linked chronic low-level inflammation in older adults to cognitive decline and dementia, including vascular dementia and Alzheimer's disease.[22]One study found that people with the highest CRP and IL-6 levels (> 2.4 pg/mL) had a ~30-40% increased risk of cognitive decline compared to those with the lowest levels (< 1.4 pg/mL).[23] Inflammatory markers can be elevated before the onset of cognitive dysfunction, indicating their potential relevance as a prognostic tool in high-risk individuals

- **Multiple sclerosis**

An autoimmune disease is caused by chronic inflammation in the central nervous system disease. Activated NF-κB is found in patients with multiple sclerosis.[24] High levels of other cytokines such as IL-1α, IL-2, IL-4, IL-6, IL-10, IFN-γ, TGF-β1, TGF-β2, and TNF-α have also been found in frozen sections of central nervous system tissue from multiple sclerosis patients.[25]

- **Vasculitis**

Vasculitis is a group of diseases in which inflammation of the blood vessels is the distinctive feature. Such inflammation can cause narrowing and weakness of the vessel linings and in some instances a tendency to form small clots affects the vessels that can result in damage to the tissues or organs being supplied by those blood vessels, including the kidney, lung, skin, nerves, or even the brain.

- **Inflammatory Bowel Disease**

Inflammatory bowel diseases are a group of inflammatory disorders of the colon and small intestine comprising in Crohn's disease (CD) and ulcerative colitis (UC). Inflammatory Bowel Diseases causes inflammation anywhere along the lining of digestive tract and often spreads deep into affected tissues. A number of cytokines /chemokines and their receptors have shown to be upregulated in patients with Inflammatory Bowel Diseases. For example, the overproduction of various cytokines such as IL-2, IL-12, IL-18, IFN-γ, and TNF-α has been well registered in patients with Crohn's Diseases.[26,27]

- **Ankylosing spondylitis**

It is a chronic inflammatory disorder of unknown origin that primarily affects the spine, sternum, and large joints in the body. The most distinctive feature of this condition is a siginificant or complete loss of flexibility in the body and spine. People with this disorder experience lower back pain, morning stiffness, and limited motion. These symptoms are commonly improved after exercise and get worsened after sleep or prolonged rest.

- **Gout**

Gout is a form of inflammatory arthritis that results from an excess of uric acid which is a chemical that is released as the body breaks down certain substances in food called purines in the blood of human body. In people with gout, uric acid crystallizes in the joints causing painful attacks in the affected body part – often, initially, a big toe.

- **Myositis**

The myositis "muscle inflammation" is caused by white blood cells called lymphocytes, which are normally supposed to protect the body's immune system. In inflammatory myopathies such as myositis, lymphocytes infiltrate the healthy muscle fibers that are destroyed and affect the functionality of muscle tissue leading to fatigue and immobility.

- **Others**

Elevated inflammatory cytokines in the circulation are associated with several other Chronic conditions, like Crohn's disease, pancreatitis.[28,29,30,31,32] Inflammation is also a cause of autoimmune diseases such as rheumatoid arthritis, in which excess levels of cytokines such as TNF-α, IL-6, IL-1β, and IL-8 are often found.[33]

Herbs as alternative source of the Treatment of Inflammatory disorders:

Medicinal plants provide an important source of new chemical substances with potential therapeutic effects. These have been used in traditional medicine for the treatment of several diseases.[34] The number of studies investigating oral herbal anti-inflammatory drugs in the treatment of osteoarthritis (OA) and low back pain is steadily increasing and an updated Cochrane Systematic Review on 'Herbal Therapy for Osteoarthritis' is expected soon[35]. Whereas in Germany, preparations from devil's claw, willow bark and nettle herb are widely used as Osteoarthirits pytomedicines.[36]Preparations from ginger[37,38,39] or salai

guggal[40] or the gamma linolenic acid (GLA) containing seed oils from evening primrose, borage or blackcurrant.[41,42,43]are less popular for the treatment of osteoarthritic pain in Europe.

NSAIDs are among the most widely used drugs worldwide. They are prescribed for orthopaedic conditions such as osteoarthritis, soft-tissue injuries and fractures etc.[45] NSAIDs are one of the best classes of drug to prevent and treat postoperative pain.[46] The use of NSAIDs is associated with many side effects, but their harmful effects on the gastrointestinal tract, the kidney and the cardiovascular system are considered as major issues with the use of these drugs[47] Inflammatory diseases including different types of rheumatic diseases are very common throughout the world. Several indigenous drugs have been described in Ayurveda for the management of inflammatory diseases[48] Combinations of pharmacologically active principles in different plant families and species often exhibit remarkable potency and tolerance, particularly in the long term treatment of chronic disorders, like rheumatic diseases[49] The greatest disadvantage in presently available potent synthetic drugs lies in their toxicity and reappearance of symptoms after discontinuation. Therefore, the screening and development of drugs for their anti-inflammatory activity is the need of hour and there are many efforts for finding anti-inflammatory drugs from indigenous medicinal plants[50]. Lipopolyssacharide (LPS) - activated macrophages are usually used for evaluating the anti-inflammatory effects of various materials. Lipopolysaccharide is a principle component of the outer membrane of Gram-negative bacteria which is an endotoxin that induces septic shock syndrome and stimulates the production of inflammatory mediators such as nitric oxide (NO), tumor necrosis factor-a (TNF-α), interleukins, prostanoids, and leukotrienes[51,52,53] It is interesting to mention that more than 70% of anti-inflammatory drugs are synthetic and among all of these plant derived prototype asprin is considered as one of the most effective analgesic and anti-inflammatory agent and commonly used in modern medicine. Several terrestrial plants have been used in traditional ayurvedic medicine for treatment and management of distinct anti-inflammatory disorders and wound healing. Such as *Boswellic serrata* (burseraceae), *curcuma long* (zingiberaceae), *Ficus racemosa* (moraceae) and*ocimum sanctum* (labiatae) and *hypericum perforatum* (clusiaceae) and their active principle constituents like boswellic acid, curcumin, racemosic acid and flavanoid and hyperforin have shown to be responsible for pharmacological action. The anti-inflammatory action of these compounds have been associated with the inhibition of prostaglandin/or leukotrienes synthesis via interfering with COX and 5-LOX enzyme or inhibiting their expression. Unlike modern allopathic drugs which are single active components that target one specific pathway, herbal medicines work in a way that depends on an orchestral approach. A plant contains a multitude of different molecules that act synergistically on targeted elements of the complex cellular pathway. Medicinal plants have been source of wide variety of biologically active compounds for many centuries and used extensively as crude material or as pure compounds for treating various disease conditions.

Conclusion:

There is powerful link between chronic diseases and inflammation. Inflammatatory biomarkers play an important role in the elevation of chronic diseases which is a critical issue and needs to be taken care of. Focusing on reducing inflammatory stress can reduce the complications of Chronic Diseases. Phytomedicines play an important role in curing these diseases, as they contain important phytoconstituents which have been proved since time immemorial beneficial in treating chronic diseases which are cost effective and free from harmful side effects.

Conflict of Interest:

There are no conflicts of interest.

References:

1. Anderson G, Horvath J. The growing burden of chronic disease in America. Public Health Rep. 2004; 119:263–70.
2. Ferrero-Miliani L, Nielsen OH, Andersen PS, *et al.* Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation.*Clin. Exp. Immunol.* 2007; 147(2): 061127015327006
3. Abbas A.B., Lichtman A.H.Basic Immunology functions and disorders of the immune syste: In Saunders Elsevier, 2009: ISBN :978-1-4160-4688-2.
4. Dandiya PC, Kulkarni SK. Introduction to pharmacology-including toxicology and practicals, *Fifth Ed., Vallabh Prakashan*, Delhi. 1995; p.131-132
5. Lucas SM, Rothwell NJ, Gibson RM. The role of inflammation in CNS injury and disease. Br J pharmacol. 2006; 147:232-S240.
6. Calixto JB, Campos MM, Otuki MF *et al.* Anti-inflammatory compounds from plant origion. Part II. Modulation of pro inflammatory cytokines, chemokines and adhesion molecules. Planta medica.2004; 70:93-103
7. Kale M, Misar AV, Dave V, *et al.* Anti-inflammatory activity of Dalbergia laceolaria bark ethanol extracts in mice and rats. Ethnopharmacol.2007; 12:300-4.
8. Hussain SP1, Hofseth LJ, Harris CC. Radical causes of cancer. Nat Rev Cancer. 2003; 3:276-285.
9. Singh T, Newman. Inflammatory markers in population studies of aging. Ageing Res Rev.2011; 10(3):319–329
10. Tomiyama H, Okazaki R, Koji Y*et al*. Elevated C-reactive protein: a common marker for atherosclerotic cardiovascular risk and subclinical stages of pulmonary dysfunction and osteopenia in a healthy population. Atherosclerosis. 2005; 178:187-192
11. Kundu, J. K., Surh, Y.-J. Inflammation: gearing the journey to cancer. Mutat Res.2008; 659(1-2):15–30.
12. Balkwill, F. Tumour necrosis factor and cancer. Nat. Rev.Cancer.2009; 9(5):361–371
13. Horinaga M, Okita H, Nakashima J, *et al.* Clinical and pathologic significance of activation of signal transducer and activator of transcription 3 in prostate cancer. Urology. 2005; 66:671-675.
14. Mora LB, Buettner R, Seigne J, *et al.* Constitutive activation of Stat3 in human prostate tumors and cell lines: direct inhibition of Stat3 signaling induces apoptosis of prostate cancer cells. Cancer Res. 2002; 62:6659-6666.
15. Tam L, McGlynn LM, Traynor P. *et al.* Expression levels of the JAK/STAT pathway in the transition from hormone-sensitive to hormone-refractory prostate cancer. Br J Cancer 2007; 97:378-383.
16. Klein B, Zhang XG, Jourdan M, et al. Interleukin-6 is a major myeloma cell growth factor in vitro and in vivo especially in patients with terminal disease. *Curr Top Microbiol Immunol*.1990; 166:23-31.
17. Nappo, F., Esposito, K., Cioffi, M., *et al.* Postprandial endothelial activation in healthy subjects and in type 2 diabetic patients: role of fat and carbohydrate meals. J Am Coll Cardiol. 2002; 39(7):1145–1150
18. Ortega Martinez de Victoria, E., Xu, X., Koska, J., *et al.* Macrophage content in subcutaneous adipose tissue: associations with adiposity, age, inflammatory markers, and whole-body insulin action in healthy Pima Indians. Diabetes. 2009; 58(2):385–393
19. Bastard, J.-P., Maachi, M., Lagathu, C., *et al.* Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur. Cytokine Netw. 2006; 17(1):4–12
20. Hong, T., Tan, A. G., Mitchell, P. A review and meta-analysis of the association between C-reactive protein and age-related macular degeneration. Surv Ophthalmol. 2011; 56(3):184–194
21. Cao D, Li H, Yi J, et al. Antioxidant properties of the mung bean flavonoids on alleviating heat stress. PloS one. 2011; 6(6):21-71
22. Singh T, Newman. Inflammatory markers in population studies of aging. Ageing Res Rev. 2011; 10(3):319–329

23. Yaffe, K., Lindquist, K., Penninx, B. W., *et al*. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003; 61(1):76–80.
24. Gveric D, Kaltschmidt C, Cuzner ML, *et al.* Transcription factor NF-kappaB and inhibitor I kappaBalpha are localized in macrophages in active multiple sclerosis lesions. J Neuropathol Exp Neurol.1998; 57:168-178.
25. Woodroofe MN, Cuzner ML. Cytokine mRNA expression in inflammatory multiple sclerosis lesions: detection by non-radioactive in situ hybridization. Cytokine 1993; 5, 583-588.
26. Rutgeerts P, Geboes K. Understanding inflammatory bowel disease--the clinician's perspective. Eur J Surg Suppl.2001; 66-72.
27. Desreumaux P, Brandt E, Gambiez L, *et al*. Distinct cytokine patterns in early and chronic ileal lesions of Crohn's disease. Gastroenterology.1997; 113:118-126.
28. Kaser, A., Tilg, H. Metabolic aspects in inflammatory bowel diseases. Curr Drug Deliv. 2011; 72:210-218.
29. Jha, R. K., Ma, Q., Sha, H., *et al.* Acute pancreatitis: a Literature review. Med Sci Monit. 2009; 15(7):RA147–56
30. Ferrucci, L., Semba, R. D., Guralnik, J. M., *et al.* Proinflammatory state, hepcidin, and anemia in older persons. Blood. 2010; 115(18):3810–3816
31. Kadetoff, D., Lampa, J., Westman, M., Andersson, M., *et al.* Evidence of central inflammation in fibromyalgia - Increased cerebrospinal fluid interleukin-8 levels. J. Neuroimmunol. 2011; 14:1-25.
32. Rolland, Y., Abellan van Kan, G., Gillette-Guyonnet, S., and Vellas, B. Cachexia versus sarcopenia.Current Opinion in Clinical Nutrition and Metabolic. Diabetes Care. 2011; 14(1):15–21
33. Deon D, Ahmed S, Tai K, *et al.*Cross-talk between IL-1 and IL-6 signaling pathways in rheumatoid arthritis synovial fibroblasts. J Immunol.2001; 167:5395-5403.
34. Wahida B, Abderrahman B, Nabil C. Antiulcerogenic activity of zizyohus lotus (L) extracts. J Ethanopharmacol. 2007; 112:228-31.
35. Little CV, parsons T, Little C. Personal communication. Herbal therapy for treating osteoarthritis. Cochrane Database Syst Rev. 2002; (1):CD002947
36. Chrubasik S. Osteoarthritis: Pharmacology and clinical indications of selected botanicals. The pain clinic. 2004; 16:1-16.
37. Bliddal H, Rosetzsky A and Schlichting P. A randomized, placebo controlled, cross over study of ginger extracts and ibuprofen in osteoarthritis. Osteoarthritis Cartilage.2000; 8:9-12.
38. Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum. 2001; 44:2531-2538.
39. Wigler I, Grotto I, Caspi D, Yaron M. The effects of Zintona EC (a ginger extract) on symptomatic gonarothritis. Osteoarthritis cartilage. 2003; 11:783-789
40. Kimmatkar N, Thawani V, Hingorani L *et al.* Efficacy and tolerability of Boswellia serata extract in treatment of osteoarthritis of knee –a randomized double blind placebo trail. Phytomedicine. 2003; 10:3-7
41. Belch JJF, Ansell D, Madhok R. Effect of altering dietary essential fatty acids on requirements for non-steroidalanti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. Ann Rheum Diseases. 1988; 47:96-104.
42. Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with black currant seed oil. Rheumatol. 1994;33:847-852
43. Zurier RB, Rossetti RG, Jacobson EW. Gamma linolenic acid treatment of rheumatoid arthritis. Arth Rheum. 1996; 39:1808-1817.
44. Boursinos LA, Karachalios T, Poultsides L *et al.* Do steroids, conventional nonsteroidal anti-inflammatory drugs and selective cox-2 inhibitors adversely affect fracture healing? J Musculoskelet Neuronal Interact. 2009; 9(1):44-52.
45. Luna SPL, Basilio AC, Steagall VMP, et al. Evaluation of adverse effects of long term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen and meloxicam in dogs. AJVR. 2007; 68(3):258-264
46. Alexandrina LD. Antibiotics and Antiseptics in Periodontal therapy: Berlin /Heidlburg, Springer verlang.2010.
47. Handa SS, Chawla AS, Sharma AK. Fitoterapia. 1992; 63(1):3-30.
48. Arens CM, Okpanyi SN. Planta Medica.1990; 56:656-657.
49. Srinivasan K, Muruganandan S, Lal J, *et al.* Evaluation of anti inflammatory activity of pongamia pinnata in rats. J. Ethanopharmacol. 2001; 78:151-157.
50. Hewett JA, Roth RA. Hepatic and extra hepatic pathobiology of bacterial lipopolysaccharides. Pharmacol Rev. 1993; 45:382-411
51. Watson WH, Zhao y, Chawla RK, S. adenosylmethionine attenuates the lipodpolysaccharide induced expression of the gene for tumour necrosis factor alpha. Biochem j. 1999; 342:21-5
52. Kubes P, Mc Cafferty DM. Nitric oxide and intestinal inflammation.Am.J. Med. 2000; 109:150-8